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JAPANESE PATENT APPLICATION (A)

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THIADIAZOLOPYRIMIDINE DERIVATIVES

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J57-142989
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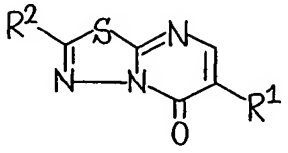
Specification

1. Title of the invention

Thiadiazolopyrimidine derivatives.

2. Patent Claims

(1) A thiadiazolopyrimidine derivative represented by general formula (I) or biologically permissible salt thereof

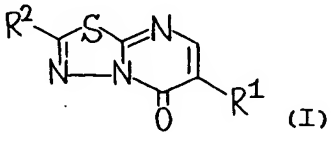


(Wherein, R^1 denotes 1 or 2H-tetrazol-5-yl group, carboxyl group or lower alkoxycarbonyl group, R^2 denotes an alkyl group, cycloalkyl group or alkylthio group of carbon number 4 or more, or an optionally substituted aryl group or heteroaryl group, and the substituents on the aryl group or heteroaryl group are selected from alkyl group, alkoxy group, alkylenedioxy group, halogen group, hydroxy group, nitro group or amino group).

(2) A compound in accordance with Claim 1 or biologically permissible salt thereof, wherein in the formula, the substituent R^1 is 1 or 2H-tetrazol-5-yl group, carboxyl group and the substituent R^2 is an alkyl group or cycloalkyl group of carbon number 4 or more, or an aryl group or heteroaryl group which may have alkyl group, alkoxy group, alkylene dioxy group, halogen group or hydroxy group as substituent.

3. Detailed explanation of the invention

This invention relates to a novel thiadiazolopyrimidine derivative represented by general formula (I) or biologically permissible salt thereof



(I)

(Wherein, R^1 denotes 1 or 2H-tetrazol-5-yl group, carboxyl group or lower alkoxycarbonyl group, R^2

denotes an alkyl group, cycloalkyl group or alkylthio group of carbon number 4 or more, or an optionally substituted aryl group or heteroaryl group. Wherein as the substituents on the aryl group or heteroaryl group, an alkyl group, alkoxy group, alkylenedioxy group, halogen group, hydroxy group, nitro group or amino group are selected).

In prior art, several species of thiadiazolopyrimidine derivatives having similar chemical structures to the compounds of this invention have been known.

However, such already known thiadiazolopyrimidine derivatives are either related to agrochemicals [Agr. Biol. Chem., 37, 1197-1201 (1978)] or antitumor agents [Agr. Biol. Chem., 41, 2047-2053 [1977]), and there is no mention of the relationship between thiadiazolopyrimidine derivatives and antiallergic action.

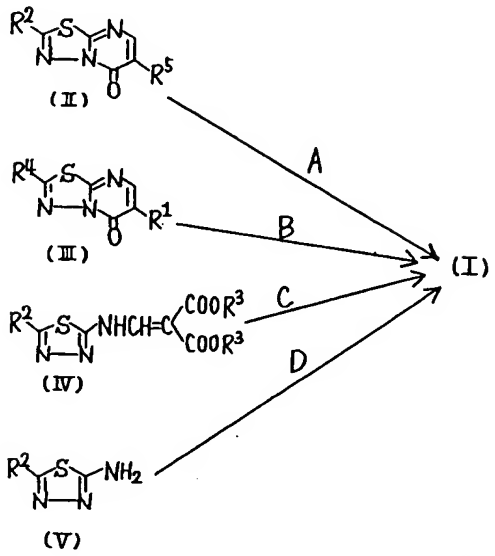
The inventors of this invention carried out assiduous investigations into compounds having antiallergic action, as a result, discovered that novel thiadiazolopyrimidine derivatives represented by formula (I) had excellent antiallergic action. This invention was completed on the basis of this discovery.

In particular, the compounds of this invention are characterized in being antiallergic agents that suppress release of chemical mediaters induced by antigen-antibody reaction, and also that the appearance of the action thereof is effectively observed by oral administration.

In prior art, as a typical agent having aforesaid action mechanism, disodium cromoglycate has been known, however, this agent does not display effectivness in oral administration, and is used by powder inhalation method. However, there are defects that the inhalation administration method is difficult to perform appropriately to infants, or application is difficult to patients sensitive to powder stimuli, therefore, a development of an excellent drugs that cyano antibody e orally administered has been desired.

Accordingly, this invention relates to the provision of compounds having a novel type of antiallergic action, and is useful for the treatment or prevention of bronchial asthma, allergic gastrointestinal disorder, hay fever, urticaria or the like due to the excellent antiallergic action thereof.

The compounds of this invention represented by formula (I) are produced by the following reaction equations.



In aforesaid equations, R^1 and R^2 have the same aforesaid meanings. R^3 denotes a lower alkyl group, R^4 denotes a group that can be converted to R^2 by reduction, halogenation or alkylation, R^5 denotes lower alkoxycarbonyl group or 2-tert-butyl-2H-tetrazol-5-yl group.

In other words, the compounds of this invention can be produced by any of the production methods of aforesaid A-D. Each production method is explained below in detail.

Production method A:

Explanations are given separately for cases wherein the substituent R^5 is 2-tert-butyl-2H-tetrazol-5-yl group (Production method A-1) and lower alkoxycarbonyl group (Production method A-2).

When the target compound is produced in accordance with Production method A-1, the compound of formula (II) is heated with acid in the presence or absence of a solvent at about 70-180°C for about 30 minutes to about 10 hours.

As the solvent that can be use, water or a high boiling point organic solvent such as Dowtherm A, sulfolane, t-butylbenzene, toluene or the like can be nominated, and as acid, an inorganic acid such as sulfuric acid, an organic acid such as p-toluene sulfonic acid, trifluoro acetic acid or the like, a Lewis acid such as boron trifluoro etherate or the like can be used.

When the target compound is produced in accordance with Production method A-2, the compound of formula (II) is subjected to hydrolysis reaction in the presence of acid or alkali at room temperature to about 130°C for about 1-24 hours.

As acid that can be used, an inorganic acid such as hydrochloric acid, sulfuric acid, hydrobromic acid or the like, an organic acid such as acetic acid, trifluoroacetic acid or the like or a mixture thereof, or a Lewis acid such as aluminium halide or the like can be exemplified, and as alkali, sodium hydroxide, potassium hydroxide or the like can be typically used. Moreover, when the substituent R^5 is methoxycarbonyl group, aluminium halide - dimethylsulfide can be used.

Production method B:

When the target compound is produced in accordance with this production method, the compound of formula (III) is subjected to reduction, halogenation or alkylation, and conventional means can be adopted for these reactions.

For example, when the substituent R^4 contains nitro group and when this is reduced, iron powder - acetic acid or the like can be used as reducing agent. For halogenation reaction, the compound is directed reacted with bromine, chlorine or the like, or other widely used halogenation agent, for example, NBS, NCS or the like can be used. Moreover, as alkylation reaction reagent, as typical species, dialkyl sulfuric acid, alkylhalide or the like are nominated.

Production method C:

When the target compound is produced in accordance with this production method, the compound of formula (IV) is heated in the presence or absence of solvent to 100-260°C, or heated in a solvent with boron trifluoride etherate to 100-250°C for about 10 minutes to about 2 hours.

As solvent that can be used, high boiling point organic solvent such as Dowtherm A, sulfolane, in addition toluene, xylene, t-butylbenzene or the like can be exemplified.

Production method D:

When the target compound is produced in accordance with this production method, the compound of formula (V) is heated in the presence or absence of solvent together with lower alkoxymethylene malonate di-lower alkyl ester to about 70-200°C for about 1-2 hours, thereafter, heated in the presence or absence of solvent to about 120-260°C, or heated in a solvent with boron trifluoride etherate to 100-200°C for about 10 minutes to about 2 hours. As solvent, the same species as in Production method C can be used.

Wherein among the starting compounds used in Production methods A-D, the compounds represented by formulae (II), (III) and (IV) are novel compounds. Moreover, a part of formula (V) includes novel compounds.

Such novel compounds can be produced by the methods described below. Production methods of starting compounds are explained briefly, below.

The novel compounds among the compounds of formula (V) can be produced in accordance with well known production method of thiadiazole derivatives. The compounds of formula (IV) can be produced by heating the compound of formula (V) and lower alkoxymethylene malonate di-lower alkyl ester in the presence or absence of solvent to about 100-150°C for about 15 minutes to 4 hours. The compound represented by formula (II) is produced by reacting the compound of formula (V) and 2-(2-t-butyl-2H-tetrazol-5-yl)-8-dimehylamino acrylate ethyl ester in acetic acid or propionic acid under reflux for about 8-25 hours, or by reacting the compound of formula (V) and lower alkoxymethylene malonate di-lower alkyl ester under reaction conditions of Production method D. The compound of

formula (III) can be produced by the same methods as in the compound of formula (II).

Wherein, among the compounds of formula (I), when R^1 is 1 or 2H-tetrazol-5-yl group or carboxyl group, an addition salt can be formed with alkali metal such as sodium, potassium or the like, alkali earth metal such as calcium or the like or amine species such as ammonia, tris (hydroxymethyl) aminomethane, N-methylglucamine or the like.

The excellent antiallergic action of the compounds of this invention produced in this way was confirmed by the measurement of suppression rate of passive cutaneous anaphylaxis reaction (PCA reaction) of allogenic rats using serum of the rat having reaginic antibody with respect to ovalbumin. As a result, the compounds of this invention were found to have potent antiallergic action by significantly suppressing the PCA reaction by oral administration as well as intravenous administration.

Wherein, sodium cromoglycate which is a well known chemical mediator suppresser (antiallergic drug) hardly suppresses aforesaid PCA reaction by oral administration. This invention is explained by the following Reference Examples and Examples.

Reference Example 1:

2-(2-t-butyl-2H-tetrazol-5-yl)-3-dimethylaminoacrylate ethyl ester

A mixture of 58.7 g 2-(2-t-butyl-2H-tetrazol-5-yl) acetate ethyl ester and 59.7 g dimethylformamide diethylacetal was heated and stirred at 100°C for 8 hours. After cooling, recrystallization was carried out from ether - petroleum ether, and thereby 50.7 g of 2-(2-t-butyl-2H-tetrazol-5-yl)-3-dimethylaminoacrylate ethyl ester having melting point of 73-75°C was obtained.

Elemental analysis value (%)	as $C_{12}H_{21}N_5O_2$		
Calculated:	C: 53.92	H: 7.92	N: 26.20
Measured:	C: 53.83	H: 7.85	N: 26.55

Reference Example 2:

2-amino-5-(2,3-dimethoxyphenyl)-1,3,4-thiadiazole

Into 250 ml EtOH were dissolved with heating, 25.0 g thiosemicarbazide and 10.0 g sodium acetate,

thereto was added 13.7 g 2,3-dimethyoxybenzaldehyde and the mixture was heated under reflux for 2 hours. After cooling, the precipitate was collected by filtration, and thereby 34.5 g of 2,3-dimethyoxybenzaldehyde thiosemicarbazone having melting point of 234-236°C was obtained.

A mixture of 34.5 g of this thiosemicarbazone, 100 l acetic anhydride and 0.1 ml pyridine were gently refluxed for 1.5 hours. After cooling, the precipitate was collected by filtration, washed with ether and thereby 44.6 g of 2-acetamino-4-acetyl-5-(2,3-dimethoxyphenyl)-4,5-dihydro-1,3,4-thiadiazole was obtained.

This dihydrothiadiazole 44.6 g was suspended in 1 litre of acetic acid, and while holding at 20°C or less, thereto was added 35.0 g potassium permanganate. After stirring for 2.5 hours, the mixture was poured in 500 ml water, and this was treated with 30 % hydrogen peroxide. The precipitate was collected by filtration, washed with water, dried and thereby 32.1 g of 2-acetamino-5-(2,3-dimethoxyphenyl)-1,3,4-thiadiazole having melting point of 291-293°C was obtained.

A mixture of 32.1 g of this acetamino body and 200 ml of 85 % hydrazine hydrate was heated to 80°C and stirred for 2 hours. After cooling, water was added, insolubles were collected by filtration, washed with water, dried and thereby 27.3 g of 2-amino-5-(2,3-dimethoxyphenyl)-1,3,4-thiadiazole having melting point of 202-205°C was obtained.

Elemental analysis value (%)	as $C_{10}H_{11}N_3O_2$		
Calculated:	C: 50.62	H: 4.67	N: 17.71
Measured:	C: 50.28	H: 4.76	N: 17.72

In the same way as in Reference Example 2, the following starting compounds of formula (V) were produced.

Reference Ex. No.	R2 of formula (V)	mp. (°C)
3	octyl	178-185
4	4-tert-butylphenyl	264
5	4-butoxyphenyl	210-211
6	2,4-dimethoxyphenyl	192-194
7	4-isobutoxy-3-methoxyphenyl	180
8	2-chloro-6-fluorophenyl	173-175
9	3-chloro-4-fluorophenyl	170-174
10	2-hydroxyphenyl	241-242
11	3-hydroxyphenyl	233-234
12	4-hydroxyphenyl	231-233
13	4-chloro-3-methylphenyl	207-211
14	3-fluoro-4-methoxyphenyl	200-202
15	4-hydroxy-3-methoxyphenyl	204-205
16	6-methoxy-2-naphthyl	248-249
17	5-chloro-2-furyl	240-243
18	5-methyl-2-thienyl	203-205
19	2-pyridinyl	263-265
20	6-methyl-2-pyridinyl	250-258
21	5-pyrimidinyl	300-305

Reference Example 22:

2-t-butyl-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one.

To 10 ml acetic acid were added 1.90 g 2-amino-5-t-butyl-1,3,4-thiadiazole and 8.20 g 2-(2-t-butyl-2H-tetrazol-5-yl)-3-dimethylamino acrylate ethyl ester, the mixture was heated under reflux for 130-140°C for 20 hours. The acetic acid was eliminated by distillation under reduced pressure, water was added to the residue, and the mixture was adjusted to weak alkaline with aqueous sodium hydrogen carbonate. The precipitate was collected by filtration, recrystallized from isopropanol, and thereby 2.90 g of 2-t-butyl-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,34] thiadiazolo [3,2-a] pyramiding-5-one having melting point of 201-202°C was obtained.

Elemental analysis value (%)	as $C_{14}H_{19}N_7OS$		
Calculated:	C: 50.43	H: 5.74	N: 29.41
Measured:	C: 50.39	H: 5.70	N: 29.28

In the same way as in Reference Example 22, the following starting compounds of formula (II) were produced (wherein, R^5 is 2-t-butyl-2H-tetrazol-5-yl group).

Ref. Ex. No.	R2 of formula (II)	mp. (°C)	
23	3,4-dichlorophenyl	249-251	
24	2-thienyl	248-249	
25	3-fluoro-4-methoxyphenyl	219-222	
26	octyl	78-79	
27	cyclohexyl	203-204	
28	isobutylthio	134	
29	4-methoxyphenyl	245-247	
30	4-butoxyphenyl	209-211	
31	2,3-dimethoxyphenyl	246-248	
32	2,4-dimethoxyphenyl	236-238	(decomp.)
33	3,4-dimethoxyphenyl	187-188	
34	3,4,5-trimethoxyphenyl	224-225	
35	4-isobutoxy-3-methoxyphenyl	215-218	
36	3,4-methylene dioxyphenyl	257-258	(decomp.)
37	2-fluorophenyl	200-230	(unclear)
38	3-fluorophenyl	178-181	
39	4-fluorophenyl	237-240	
40	3-chlorophenyl	217-220	
41	3,5-dichlorophenyl	213-215	
42	2-chloro-6-fluorophenyl	176-178	
43	3-chloro-4-fluorophenyl	250-252	
44	2-hydroxyphenyl	251-254	(decomp.)
45	3-hydroxyphenyl	246-248	(decomp.)
46	4-hydroxyphenyl	264-265	(decomp.)
47	4-chloro-3-methylphenyl	205-207	(decomp.)
48	4-hydroxy-3-methoxyphenyl	243-245	(decomp.)
49	2-naphthyl	255-257	(decomp.)
50	6-methoxy-2-naphthyl	249-251	(decomp.)
51	2-furyl	230-232	
52	5-chloro-2-furyl	219-221	
53	5-bromo-2-furyl	230-232	
54	5-methyl-2-thienyl	266-268	
55	5-pyrimidinyl	245-248	
56	phenyl	233-233.5	
57	4-methylphenyl	253-255	(decomp.)
58	4-tert-butylphenyl	206.5	
59	2-chlorophenyl	184-187	
60	4-chlorophenyl	234-238	
61	4-nitrophenyl	285-287	(decomp.)
62	2-pyridinyl	255-258	
63	3-pyridinyl	236-239	
64	4-pyridinyl	279-282	
65	6-methyl-2-pyridinyl	268-270	(decomp.)

Reference Example 66:

2-(5-bormo-2-thienyl)-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,34] thiadiazolo [3,2-a] pyramiding-5-one

To a mixture of 3.13 g 2-(2-thienyl)-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one, 5.00 g sodium acetate and 50 ml acetic acid was added 2.0 ml bromine, the mixture was gently refluxed for 4 hours. After cooling, water was added, and neutralized with sodium carbonate. The precipitate was recovered by filtration, recrystallized from ethanol, and thereby 2.67 g of 2-(5-bormo-2-thienyl)-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,34] thiadiazolo [3,2-a] pyramiding-5-one with melting point of 253-256°C was obtained.

Reference Example 67:

2-(4-aminophenyl)-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,34] thiadiazolo [3,2-a] pyramiding-5-one

In 100 ml acetic acid was dissolved 2.0 g 2-(4-nitrophenyl)-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one, and while holding at 90-100°C, thereto was added 3.0 g of iron powder. Thereafter, the mixture was stirred at the same temperature for 1 hour, thereafter, insolubles were eliminated by filtration. The filtrate was concentrated under reduced pressure, the concentrate was poured on water, the precipitate was recovered by filtration, recrystallized from chloroform - ethanol, and thereby 1.30 g of 2-(4-aminophenyl)-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,34] thiadiazolo [3,2-a] pyramiding-5-one having melting point of 269-270°C was obtained.

Reference Example 68:

[5-(2-chlorophenyl)-1,3,4-thiadiazol-2-yl] aminomethylene malonate diethyl ester

A mixture of 6.28 g 2-amino-5-(2-chlorophenyl)-1,3,4-thiadiazol and 8.64 g ethoxymethylene malonate diethyl ester was heated and stirred at 140°C for 2.5 hours. After cooling, recrystallization was carried out from ethanol, and thereby 6.20 g of [5-(2-chlorophenyl)-1,3,4-thiadiazol-2-yl] aminomethylene malonate diethyl ester having melting point of 113-118°C was obtained.

Elemental analysis value (%)	as $C_{16}H_{16}ClN_3O_4S$		
Calculated:	C: 50.33	H: 4.22	N: 11.00
Measured:	C: 49.91	H: 4.07	N: 11.11

In the same way as in Reference Example 68, the following starting compounds of formula (IV) were produced.

Ref. Ex. No.	R2	R3	mp. (°C)
69	4-fluorophenyl	methyl	166-168

70	3,4-dimethoxyphenyl	ethyl	160-161
71	ethylthio	ethyl	51-62
72	isobutylthio	ethyl	75-76.5
73	phenyl	ethyl	155-157
74	4-methylphenyl	ethyl	156
75	4-tert-butylphenyl	ethyl	138.5
76	4-methoxyphenyl	ethyl	129-130
77	3-chlorophenyl	ethyl	155-157
78	4-chlorophenyl	ethyl	137-139
79	3,4-dichlorophenyl	ethyl	167-169
80	3,4-dichlorophenyl	ethyl	142-145
81	4-nitrophenyl	ethyl	185-186
82	2-naphthyl	ethyl	138-139
83	2-furyl	ethyl	100-101
84	3-pyridinyl	ethyl	145-147
85	4-pyridinyl	ethyl	119-120
86	5-pyrimidinyl	ethyl	162-164
87	ethylthio	methyl	67-71
88	isobutylthio	methyl	82-84
89	4-methylphenyl	methyl	157
90	4-tert-butylphenyl	methyl	144
91	4-methoxyphenyl	methyl	156-158
92	2-chlorophenyl	methyl	120-130
93	3-chlorophenyl	methyl	149-151
94	4-chlorophenyl	methyl	188-192
95	3,4-dichlorophenyl	methyl	174-177
96	3,5-dichlorophenyl	methyl	192-195
97	2-naphthyl	methyl	186-188
98	2-furyl	methyl	206-208
99	2-thienyl	methyl	185-188
100	3-pyridinyl	methyl	224-226
101	4-pyridinyl	methyl	168-170
102	5-pyrimidinyl	methyl	253-256
103	3,4,5-trimethoxyphenyl	ethyl	103-105
104	3,4-methylene dioxyphenyl	ethyl	171-172
105	4-fluorophenyl	ethyl	162-163
106	3,4,5-trimethoxy phenyl	methyl	157-159
107	3,4-methylene dioxyphenyl	methyl	186-187
108	5-chloro-3-furyl	methyl	145-146
109	cyclohexyl	ethyl	83-84
110	3,4-dimethoxy phenyl	methyl	185-187

Example 1:

2-t-butyl-6-(1 or 2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one

In 2 ml sulfolane was dissolved 2-t-butyl-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one, thereto was added 0.10 g p-toluene sulfonic acid, the mixture was heated and stirred at 160-170°C for 2 hours. After cooling, water was added, the precipitate was recovered by filtration, recrystallized from dimethylformamide, and thereby 0.31 g of 2-t-butyl-6-(1 or 2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one having melting point of 290°C or more was obtained.

Elemental analysis value (%)	as $C_{10}H_{11}N_7OS$		
Calculated:	C: 43.31	H: 4.00	N: 35.36
Measured:	C: 43.35	H: 3.94	N: 35.28

In the same way as in Example 1, the following target compounds of formula (I) were produced (wherein, R^1 is 1 or 2H-tetrazol-5-yl group).

Ex. No.	R2	mp. (°C)	Molecular formula	Elemental analysis value Calculated / Measured		
				C	H	N
2	octyl	217-219	C14H19N7OS	50.43/ 50.60	5.74/ 58.2	29.41/ 29.17
3	cyclohexyl	262-268 (decomp.)	C12H13N7OS	47.51/ 47.54	4.32/ 4.58	32.33/ 32.16
4	isobutylthio	258-260 (decomp.)	C10H11N7OS2	38.82/ 39.26	3.58/ 3.84	31.70/ 31.18
5	4-methoxy phenyl	283-285 (decomp.)	C13H9N7O2S	47.70/ 48.11	2.77/ 3.18	29.86/ 29.97
6	4-butoxy phenyl	260-262	C16H15N7O2S	52.02/ 52.09	4.09/ 4.04	26.54/ 26.55
7	2,3-dimethoxy phenyl	285-287 (decomp.)	C14H11N7O3S	47.05/ 47.04	3.10/ 3.30	27.44/ 27.50
8	2,4-dimethoxy phenyl	295-298 (decomp.)	C14H11N7O3S	47.05/ 47.41	3.10/ 3.35	27.44/ 27.63
9	3,4-dimethoxy phenyl	>290	C14H11N7O3S	47.05/ 47.32	3.10/ 3.30	27.44/ 27.44
10	3,4,5-trimethoxy phenyl	275-277 (decomp.)	C15H13N7O4S	46.51/ 46.72	3.38/ 3.62	25.31/ 25.47
11	4-isobutoxy-3-methoxyphenyl	297-299 (decomp.)	C17H17N7O3S	51.11/ 51.02	4.29/ 4.37	24.55/ 24.81
12	3,4-methylene dioxyphenyl	>300	C13H7N7O3S	45.74/ 45.74	2.07/ 2.39	28.78/ 28.94
13	2-fluorophenyl	>310	C12H6FN7OS	45.71/ 45.75	1.92/ 2.26	31.10/ 31.10
14	3-fluorophenyl	>300	C12H6FN7OS	45.71/	1.92/	31.10/

				45.80	2.10	31.10
15	4-fluorophenyl	>300	C12H6FN7OS	45.71/	1.92/	31.10/
				45.98	2.27	31.02
16	3-chlorophenyl	>300	C12H6ClN7OS	43.45/	1.82/	29.56/
				43.62	2.02	29.46
17	3,5-dichloro phenyl	>300	C12H5Cl2N7OS	39.36/	1.38/	26.78/
				39.49	1.83	26.93
18	2-chloro-6-fluoro phenyl	>310	C12H5ClFN7OS	41.21/	1.44/	28.04/
				41.34	1.68	28.08
19	3-chloro-4-fluoro phenyl	295-298 (decomp.)	C12H5ClFN7OS	41.21/	1.44/	28.04/
				40.46	1.81	27.23
20	2-hydroxy phenyl	>300	C12H7N7O2S	46.00/	2.25/	31.30/
				45.85	2.38	30.95
21	3-hydroxy phenyl	>300	C12H7N7O2S	46.00/	2.25/	31.30/
				46.31	2.15	31.08
22	4-hydroxy phenyl	>300	C12H7N7O2S	46.00/	2.25/	31.30/
				45.69	2.52	30.91
23	4-chloro-3-methylphenyl	310-315 (decomp.)	C13H5ClN7OS	45.15/	2.33/	28.36/
				45.37	2.55	28.28
24	4-hydroxy-3-methoxyphenyl	>300	C13H9N7O3S	45.48/	2.64/	28.56/
				45.64	2.98	28.49
25	2-naphthyl	>300	C16H9N7OS	55.32/	2.61/	28.23/
				55.27	2.96	28.13
26	6-methoxy-2-naphthyl	300-303 (decomp.)	C17H11N7O2S	54.10/	2.94/	25.98/
				54.27	3.21	26.09
27	2-furyl	>300	C10H5N7O2S	41.81/	1.75/	34.13/
				41.94	2.03	33.74
28	5-chloro-2-furyl	>300	C10H4BrN7O2S	33.35/	1.12/	25.56/
				33.07	1.67	26.68
29	5-bromo-2-furyl	>300	C10H4BrN7O2S	33.35/	1.12/	25.56/
				33.07	1.67	26.68
30	5-methyl-2-thienyl	>300	C11H7N7OS2	41.63/	2.22/	30.90/
				41.71	2.60	30.79
31	5-bromo-2-thienyl	>300	C10H4BrN7O2S	31.50/	1.06/	25.72/
				31.64	1.56	25.78
32	5-pyrimidinyl	>300	C10H5N9OS	40.13/	1.68/	42.12/
				39.60	2.19	41.90

Example 33:

2-(3,4-dichlorophenyl)-6-(1 or 2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one

To 7.5 ml concentrated sulfuric acid was added 3.10 g 2-(3,4-dichlorophenyl)-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one, the mixture was heated and stirred at 100-110°C for 3 hours. After cooling, iced water was added, the precipitate was recovered by filtration, recrystallized from dimethylformamide, and thereby 1.70 g of 2-(3,4-dichlorophenyl)-6-(1 or 2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one having melting point of 295-300°C was obtained.

Elemental analysis value (%)	as $C_{12}H_5Cl_2N_7OS$		
Calculated:	C: 39.36	H: 1.38	N: 26.78
Measured:	C: 39.54	H: 1.64	N: 26.88

In the same way as in Example 33, the following compounds of formula (I) were produced (wherein, R^1 is 1 or 2H-tetrazol-5-yl group).

Ex. No.	R2	mp. (°C)	Molecular formula	Elemental analysis value Calculated / Measured C	H	N
34	phenyl	>300	C12H7N7OS	48.47/ 48.65	2.37/ 2.73	32.98/ 32.52
35	4-methyl phenyl	>300	C13H9N7OS	50.15/ 50.35	2.91/ 3.11	31.50/ 31.73
36	4-tert-butyl phenyl	280-282 (decomp.)	C16H15N7OS	54.37/ 54.59	4.28/ 4.57	27.75/ 27.54
37	2-chlorophenyl	>300	C12H6ClN7OS	43.45/ 43.67	1.82/ 2.18	29.56/ 29.61
38	4-chlorophenyl	>300	C12H6ClN7OS	43.45/ 43.44	1.82/ 2.01	29.56/ 29.73
39	4-nitrophenyl	293-295 (decomp.)	C12H6N8O3S	42.10/ 42.66	1.77/ 2.10	32.74/ 32.72
40	4-aminophenyl	>300	C12H6N8OS	46.15/ 46.24	2.58/ 2.81	35.88/ 35.36
41	2-pyridinyl	>310	C11H6N8OS	44.29/ 44.43	2.03/ 2.40	37.57/ 37.84
42	3-pyridinyl	>300	C11H6N8OS	44.29/ 44.47	2.03/ 2.25	37.57/ 37.47
43	4-pyridinyl	>300	C11H6N8OS	44.29/ 44.67	2.03/ 2.39	37.57/ 37.43
44	6-methyl-2-pyridinyl	275-280 (decomp.)	C12H8N5OS	46.15/ 46.31	2.58/ 2.43	35.88/ 35.64

Example 45:

2-(2-thienyl)-6-(1 or 2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one

A mixture of 2.00 g 2-(2-thienyl)-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one, 20 ml Dowtherm A and 1 ml boron trifluoride etherate was heated and stirred at 170°C for 30 minutes. After cooling, the precipitate was recovered by filtration, recrystallized from dimethylformamide, and thereby 1.03 g of 2-(2-thienyl)-6-(1 or 2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one having melting point of 300°C or more was obtained.

Elemental analysis value (%)	as $C_{10}H_5N_7OS$		
Calculated:	C: 39.59	H: 1.66	N: 32.33
Measured:	C: 39.83	H: 2.10	N: 32.22

Example 46:

2-(3-fluoro-4-methoxyphenyl)-6-(1 or 2H-tetrazol-5-yl)-5H[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one

To 10 ml of 50 % trifluoroacetic acid was added 0.50 g 2-(3-fluoro-4-methoxyphenyl)-6-(2-t-butyl-2H-tetrazol-5-yl)-5H-[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one and the mixture was heated under reflux for 5 hours. Trifluoroacetic acid was eliminated by distillation under reduced pressure. Insolubles were recovered by filtration, recrystallized from dimethylformamide, and thereby 0.26 g of 2-(3-fluoro-4-methoxyphenyl)-6-(1 or 2H-tetrazol-5-yl)-5H[1,3,4] thiadiazolo [3,2-a] pyramiding-5-one having melting point of 298-300°C (decomposition) was obtained.

Elemental analysis value (%)	as $C_{13}H_8FN_7O_2S$		
Calculated:	C: 45.21	H: 2.34	N: 28.39
Measured:	C: 45.34	H: 2.83	N: 28.06

Example 47:

2-(5-methyl-2-thienyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carnoxylic acid ethyl ester

A mixture of 2.69 g 2-amino-5-(5-methyl-2-thienyl)-1,3,4-thiaziazole and 3.23 g ethoxymethylene malonate diethyl ester was heated and stirred at 120-130°C for 1.5 hours. Thereto was added 10 ml Dowtherm A, and while holding at 120°C, thereto was added 1.5 ml boron trifluoride etherate, and the mixture was held at the same temperature for 1 hour. After cooling, ethanol was added, the precipitate was recovered by filtration, recrystallized from chloroform - ethanol and thereby 2.50 g of 2-(5-methyl-2-thienyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carnoxylic acid ethyl ester

having melting point of 190-191°C was obtained.

Elemental analysis value (%)	as $C_{13}H_{11}N_3O_3S_2$		
Calculated:	C: 48.58	H: 3.45	N: 13.08
Measured:	C: 48.58	H: 3.47	N: 13.01

In the same way as in Example 47, the following compounds of formula (I) were produced (wherein, R^1 = $COOR^3$).

Ex. No.	R2	R3	mp. (°C)	Molecular formula	Elemental analysis value Calculated/Measured C	H	N
48	octyl	ethyl	95-97	C16H23N3O3S	56.95/ 57.09	6.87/ 6.88	12.45/ 12.26
49	4-isobutoxy-3-methoxyphenyl	ethyl	210-211	C19H21N3O5S	56.56/ 56.52	5.25/ 5.22	10.42/ 10.40
50	3-fluorophenyl	ethyl	166-169	C14H10FN3O3S	52.66/ 52.85	3.16/ 3.45	13.16/ 12.86
51	2-hydroxy phenyl	ethyl	291-294 (decomp.)	C14H11N3O4S	52.99/ 52.94	3.49/ 3.51	13.24/ 13.22
52	3-hydroxy phenyl	ethyl	249-252	C14H11N3O4S	52.99/ 53.15	3.49/ 3.62	13.24/ 13.26
53	4-hydroxy phenyl	ethyl	282-284 (decomp.)	C14H11N3O4S	52.99/ 53.26	3.49/ 3.58	13.24/ 13.47
54	4-hydroxy-3-methoxyphenyl	ethyl	232-234	C15H13N3O5S	51.87/ 51.70	3.77/ 3.94	12.10/ 12.10
55	5-chloro-2-furyl	ethyl	208-210	C12H13ClN3O4S	44.25/ 44.23	2.48/ 2.55	12.90/ 12.61
56	octyl	methyl	105	C15H21N3O3S	55.70/ 55.69	6.55/ 6.40	12.99/ 13.00
57	4-isobutoxy-3-methoxyphenyl	methyl	228	C18H19N3O5S	55.51/ 55.96	4.92/ 4.79	10.79/ 10.71
58	2-hydroxy phenyl	methyl	282-285 (decomp.)	C13H9N3O4S	51.48/ 51.49	2.99/ 3.11	13.86/ 13.94
59	3-hydroxy phenyl	methyl	272-274	C13H9N3O4S	51.48/ 51.43	2.99/ 3.15	13.86/ 13.94
60	4-hydroxy phenyl	methyl	267-269 (decomp.)	C13H9N3O4S	51.48/ 50.99	2.99/ 3.07	13.86/ 13.73
61	4-hydroxy-3-methoxyphenyl	methyl	273-275	C14H11N3O5S	50.44/ 50.32	3.33/ 3.37	12.61/ 12.65
62	5-methyl-2-thienyl	methyl	211-213	C12H9N3O3S2	46.93/ 47.19	2.95/ 2.93	13.67/ 13.92

Example 63:

2-(2,3-dimethoxyphenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid ethyl ester

To 2 ml Dowtherm A were added 4.74 g 2-amino-5-(2,3-dimethoxyphenyl)-1,3,4-thiadiazole and 4.50 g ethoxymethylene malonate diethyl ester, the mixture was heated to 130°C for 2 hours. Thereto was further added 4 ml Dowtherm A, the mixture was heated to 120°C, thereto was added 5 ml boron trifluoride etherate, and the mixture was further heated to the same temperature for 1 hour. Ethanol was added, the mixture was cooled, thereafter, the precipitate was recovered by filtration, recrystallized from chloroform - ethanol, and thereby 6.10 g of 2-(2,3-dimethoxyphenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester having melting point of 188-190°C was obtained.

Elemental analysis value (%)	as $C_{16}H_{15}N_3O_5S$		
Calculated:	C: 53.18	H: 4.18	N: 11.63
Measured:	C: 52.99	H: 4.15	N: 11.61

In the same way as in Example 63, the following compounds of formula (I) were produced (wherein, R^1 = -$COOR^3$).

Ex. No.	R2	R3	mp. (°C)	Molecular formula	Elemental analysis value Calculated/Measured		
					C	H	N
64	4-butoxyphenyl	ethyl	147-149	C18H19N3O4S	57.89/ 57.95	5.13/ 5.03	11.25/ 11.28
65	2,4-dimethoxy phenyl	ethyl	220-222	C16H15N3O5S	53.18/ 52.94	4.18/ 4.32	11.63/ 11.61
66	2-fluorophenyl	ethyl	160-161	C14H10FN3O3S	52.66/ 52.58	3.16/ 3.29	13.16/ 13.12
67	2-chloro-6-fluorophenyl	ethyl	213-215	C14H9ClFN3O3S	47.53/ 47.25	2.56/ 2.55	11.88/ 11.88
68	4-chloro-3-methylphenyl	ethyl	205-207	C15H12ClN3O3S	51.50/ 51.73	3.46/ 3.52	12.01/ 12.01
69	3-fluoro-4-methoxyphenyl	ethyl	214-216	C15H12FN3O4S	51.57/ 51.97	3.46/ 3.55	12.03/ 12.11
70	5-bromo-2-furyl	ethyl	228-231	C12H6BrN3O4S	38.93/ 38.92	2.18/ 2.21	11.35/ 11.36
71	4-butoxyphenyl	ethyl	188-189	C17H17N3O4S	56.81/ 57.03	4.77/ 4.80	11.69/ 11.89
72	2,3-dimethoxy phenyl	methyl	281-283	C15H13N3O5S	51.87/ 51.68	3.77/ 3.80	12.10/ 12.08
73	2,4-dimethoxy phenyl	methyl	261-263	C15H13N3O5S	51.87/ 51.55	3.77/ 3.88	12.10/ 11.96
74	2-fluorophenyl	methyl	178-180	C13H8FN3O3S	51.14/ 51.11	2.64/ 2.77	13.76/ 13.78
75	3-fluorophenyl	methyl	217-219	C13H8FN3O3S	51.44/ 51.10	2.64/ 2.61	13.76/ 13.64
76	2-chloro-6-fluorophenyl	methyl	208-210	C13H7ClFN3O3S	45.96/ 45.88	2.08/ 2.13	12.37/ 12.40
77	4-chloro-3-methylphenyl	methyl	209-211	C14H10ClN3O3S	20.08/ 50.28	3.00/ 3.05	12.51/ 12.49
78	3-fluoro-4-methoxyphenyl	methyl	235-238	C14H10FN3O4S	50.15/ 50.47	3.01/ 3.09	12.53/ 12.52
79	5-bromo-2-furyl	methyl	269-273	C11H6BrN3O4S	37.09/ 37.35	1.70/ 1.84	11.80/ 11.94

Example 80:

2-t-butyl-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid methyl ester

A mixture of 2.20 g 2-amino-5-t-butyl-1,3,4-thiadiazole and 2.40 g methoxymethylene malonate dimethyl ester was heated to 110-120°C for 1 hour, thereafter, was further heated to 170-180°C for 1.5 hours. After cooling, recrystallization was carried out from isopropanol and thereby 2.60 g of 2-t-butyl-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate methyl ester having melting point of 136-137°C was obtained.

Elemental analysis value (%)	as $C_{11}H_{13}N_3O_3S$		
Calculated:	C: 49.42	H: 4.90	N: 15.72
Measured:	C: 49.22	H: 4.69	N: 15.53

Example 81

In the same way as in Example 80, a compound of formula (I) wherein R^1 was methoxycarbonyl group and R^2 was cyclohexyl group, was produced. Melting point, 157-159°C.

Elemental analysis value (%)	as $C_{13}H_{15}N_3O_3S$		
Calculated:	C: 53.22	H: 5.15	N: 14.32
Measured:	C: 53.14	H: 5.32	N: 14.33

Example 82:

2-(6-methyl-2-pyrimidinyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid methyl ester

To 10 ml of Dowtherm A were added 1.92 g 2-amino-5-(6-methyl-2-pyrimidinyl)-1,3,4-thiadiazole and 1.74 g methoxymethylene malonate dimethyl ester, the mixture was heated to 120-140°C for 1 hour, thereafter this was further heated to 220-240°C for 15 minutes. Ethanol was added, the mixture was cooled, thereafter, the precipitate was recovered by filtration, recrystallized from chloroform - ethanol, and thereby 2.04 g of 2-(6-methyl-2-pyrimidinyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate methyl ester having melting point of 228-230°C was obtained.

Elemental analysis value (%)	as $C_{13}H_{10}N_4O_3S$		
Calculated:	C: 51.65	H: 3.33	N: 18.53
Measured:	C: 51.89	H: 3.48	N: 18.48

Example 83

In the same way as in Example 82, a compound of formula (I) wherein R^1 was ethoxycarbonyl group and R^2 was 6-methyl-2-pyridinyl group, was produced. Melting point, 219-221°C.

Elemental analysis value (%)	as $C_{14}H_{12}N_4O_3S$		
Calculated:	C: 53.15	H: 3.83	N: 17.71
Measured:	C: 52.89	H: 3.83	N: 17.64

Example 84:

2-(2-pyridinyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid ethyl ester

To 0.5 ml sulfolane were added 2.67 g 2-amino-5-(2-pyrimidinyl)-1,3,4-thiadiazole and 3.24 g ethoxymethylene malonate diethyl ester, the mixture was heated to 120°C for 1 hour> Next, thereto was added 15 ml Dowtherm A, the mixture was heated under reflux for 1 5 minutes. After cooling, the precipitate was recovered by filtration, recrystallized from chloroform - ethanol, and thereby 3.28 g of 2-(2-pyridinyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester having melting point of 214-215°C was obtained.

Elemental analysis value (%)	as $C_{13}H_{10}N_4O_3S$		
Calculated:	C: 51.65	H: 3.33	N: 18.53
Measured:	C: 51.45	H: 3.48	N: 18.55

Example 85

In the same way as in Example 84, a compound of formula (I) wherein R^1 was methoxycarbonyl group and R^2 was 2-pyridinyl group, was produced. Melting point, 228-230°C.

Elemental analysis value (%)	as $C_{12}H_8N_4O_3S$		
Calculated:	C: 49.99	H: 2.80	N: 19.44
Measured:	C: 49.90	H: 2.99	N: 19.26

Example 86:

2-(2-thienyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester

To 3.66 g 2-amino-5-(2-thienyl)-1,3,4-thiadiazole was added 4.76 g ethoxymethylene malonate diethyl ester and the mixture was heated to 120-140°C for 1 hour. Next, thereto was added 60 ml

Dowtherm A, the mixture was heated under reflux for 10 minutes. After cooling, ether was added, the precipitate was recovered by filtration, recrystallized from chloroform - ethanol, and thereby 5.02 g of 2-(2-thienyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester having melting point of 170-172°C was obtained.

Elemental analysis value (%)	as $C_{12}H_9N_3O_3S_2$		
Calculated:	C: 46.89	H: 2.95	N: 13.67
Measured:	C: 47.05	H: 3.08	N: 13.76

Example 87:

2-(2-chlorophenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester

To 30 ml of Dowtherm A which had been heated under reflux, was added 6.00 g [5-(2-chlorophenyl)-1,3,4-thiadiazol-2-yl] aminomethylene malonate diethyl ester, and the mixture was heated under reflux for 2 hours. After cooling, hexane was added, the precipitate was recovered by filtration, recrystallized from ethanol, and thereby 3.85 g of 2-(2-chlorophenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester having melting point of 160-163°C was obtained.

Elemental analysis value (%)	as $C_{14}H_{10}ClN_3O_3S$		
Calculated:	C: 50.08	H: 3.00	N: 12.51
Measured:	C: 50.15	H: 3.23	N: 12.68

In the same way as in Example 87, the following target compounds of formula (I) were produced (wherein, $R^1 = COOR^3$).

Ex. No.	R2	R3	mp. (°C)	Molecular formula	Elemental analysis value Calculated/Measured C	H	N
88	ethylthio	ethyl	109	C10H11N3O3S2	42.09/ 41.85	3.89/ 3.86	14.78/ 14.49
89	isobutylthio	ethyl	73	C12H15N3O3S2	45.99/ 45.57	4.82/ 5.15	13.41/ 13.11
90	phenyl	ethyl	177-179	C14H11N3O3S	55.80/ 55.79	3.68/ 3.72	13.95/ 13.93
91	4-methylphenyl	ethyl	188	C15H13N3O3S	57.13/ 57.15	4.15/ 4.26	13.33/ 13.29
92	4-tert-butyl phenyl	ethyl	248	C18H19N3O3S	60.48/ 60.40	5.36/ 5.40	11.76/ 11.69
93	4-methoxy phenyl	ethyl	202-204	C15H13N3O4S	54.37/ 54.26	3.95/ 4.10	12.68/ 42.69
94	3-chlorophenyl	ethyl	180-183	C14H10ClN3O3S	50.08/ 49.90	3.00/ 3.05	12.51/ 12.27
95	4-chlorophenyl	ethyl	267-268	C14H10ClN3O3S	50.08/ 50.16	3.00/ 3.03	12.51/ 12.51
96	3,4-dichloro phenyl	ethyl	237-239	C14H9Cl2N3O3S	45.42/ 45.64	2.45/ 2.46	11.35/ 11.51
97	3,5-dichloro phenyl	ethyl	230-232	C14H9Cl2N3O3S	45.42/ 45.43	2.45/ 2.69	11.35/ 11.37
98	4-nitrophenyl	ethyl	295-305	C14H10N4O5S	48.55/ 48.36	2.91/ 2.94	16.18/ 16.31
99	2-naphthyl	ethyl	208-210	C18H13N3O3S	49.48/ 49.19	3.11/ 2.98	14.48/ 14.48
100	2-furyl	ethyl	197-198	C12H9N3O4S	49.48/ 49.19	3.11/ 2.98	14.43/ 14.48
101	3-pyridinyl	ethyl	198-200	C13H10N4O3S	51.65/ 51.37	3.33/ 3.34	18.53/ 18.61
102	4-pyridinyl	ethyl	248-249	C13H10N4O3S	51.65/ 51.53	3.33/ 3.20	18.53/ 18.47
103	5-pyrimidinyl	ethyl	195-198	C12H9N5O3S	47.52/ 47.58	2.99/ 3.09	23.09/ 23.04
104	ethylthio	methyl	166	C9H9N3O3S2	39.84/ 39.65	3.34/ 3.51	15.49/ 15.12
105	isobutylthio	methyl	83	C11H13N3O3S2	44.13/ 44.26	4.38/ 4.43	14.04/ 13.90
106	4-methyl phenyl	methyl	226	C14H11N3O3S	55.80/ 55.96	3.68/ 3.83	13.95/ 14.00
107	4-tert-butyl phenyl	methyl	243	C17H17N3O3S	59.46/ 59.44	4.99/ 4.99	12.24/ 12.21
108	4-methoxy	methyl	228-229	C14H11N3O4S	52.99/	3.49/	13.24/

	phenyl				53.09	3.56	13.55
109	2-chlorophenyl	methyl	206-207	C13H8ClN3O3S	48.53/ 48.56	2.51/ 2.66	13.06/ 13.17
110	3-chlorophenyl	methyl	223-226	C13H8ClN3O3S	48.53/ 48.55	2.51/ 2.80	13.06/ 12.80
111	4-chlorophenyl	methyl	273-275	C13H8ClN3O3S	48.53/ 48.20	2.51/ 2.66	13.06/ 13.29
112	3,4-dichloro phenyl	methyl	253-256	C13H7Cl2N3O3S	43.84/ 43.79	1.98/ 1.99	11.80/ 11.88
113	3,5-dichloro phenyl	methyl	260-264	C13H7Cl2N3O3S	43.84/ 43.76	1.98/ 2.14	11.80/ 11.78
114	2-naphthyl	methyl	274-277	C17H11N3O3S	60.52/ 60.50	3.29/ 3.30	12.46/ 12.67
115	2-furyl	methyl	253-254	C11H7N3O4S	47.65/ 47.52	2.54/ 2.75	15.16/ 15.27
116	2-thienyl	methyl	254-256	C11H7N3O3S2	45.04/ 45.00	2.41/ 23.9	14.33/ 14.33
117	3-pyridinyl	methyl	221-223	C128N4O3S	49.99/ 49.94	2.80/ 2.94	19.44/ 19.52
118	4-pyridinyl	methyl	230-233	C128N4O3S	49.99/ 50.35	2.80/ 3.13	19.44/ 19.19
119	5-pyrimidinyl	methyl	256-258	C11H7N5O3S	45.67/ 45.65	2.44/ 2.57	24.21/ 24.15

Example 120:

2-(4-fluorophenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate methyl ester

To 10 ml Dowtherm A was added 0.92 g [5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl] aminomethylene malonate dimethyl ester and the mixture was heated to 100°C,. Thereto was added 0.5 ml boron trifluoride etherate and the mixture was heated to the same temperature for 0.5 hours. Methanol was added, the mixture was cooled, the precipitate was recovered by filtration, recrystallized from dimethylformamide, and thereby 0.73 g of 2-(4-fluorophenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate methyl ester having melting point of 258-260°C was obtained.

Elemental analysis value (%)	as $C_{15}H_8FN_3O_3S$		
Calculated:	C: 51.14	H: 2.64	N: 13.76
Measured:	C: 51.13	H: 2.76	N: 13.89

In the same way as in Example 120, the following compounds of formula (I) were produced (wherein, $R^1 = COOR^3$).

Ex. No.	R2	R3	mp. (°C)	Molecular formula	Elemental analysis value Calculated/Measured C	H	N
121	3,4,5-trimethoxy phenyl	ethyl	202-203	C17H17N3O5S	52.16/ 51.94	4.38/ 4.29	10.74/ 10.73
122	3,4-methylene dioxyphenyl	ethyl	248-249	C15H11N3O5S	52.17/ 52.20	3.21/ 3.35	12.17/ 12.27
123	4-fluorophenyl	ethyl	261-264	C14H10FN3O3S	52.66/ 42.72	31.6/ 3.15	13.16/ 13.31
124	3,4,5-trimethoxy phenyl	methyl	217-218	C16H15N3O6S	50.92/ 50.82	4.01/ 3.92	11.14/ 11.10
125	3,4-methylene dioxyphenyl	methyl	252-253	C14H9N3O5S	50.75/ 50.63	2.74/ 2.80	12.68/ 12.57
126	5-chloro-2-furyl	methyl	218-220	C11H6ClN3O4S	42.38/ 41.91	1.94/ 2.05	13.48/ 13.83

Example 127:

2-(3,4-dimethoxyphenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester

A [5-(3,4-dimethoxyphenyl)-1,3,4-thiadiazol-2-yl] aminomethylene malonate diethyl ester 3.70 g was heated to 180-190°C for 2.5 hours. After cooling, recrystallization was carried out from dimethylformamide - ethanol, and thereby 2.50 g of 2-(3,4-dimethoxyphenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester having melting point of 209-210°C was obtained.

Elemental analysis value (%)	as $C_{16}H_{15}N_3O_5S$		
Calculated:	C: 53.18	H: 4.18	N: 11.63
Measured:	C: 52.96	H: 4.26	N: 11.60

In the same way as in Example 127, the following compounds of formula (I) were produced (wherein, $R^1 = COOR^3$).

Ex. No.	R2	R3	mp. (°C)	Molecular formula	Elemental analysis value Calculated/Measured C	H	N
128	cyclohexyl	ethyl	112-113	C14H17N3O3S	54.70/ 54.66	5.58/ 5.43	13.67/ 43.71
129	3,4-dimethoxy phenyl	methyl	234-235	C15H15N3O5S	51.87/ 51.72	3.77/ 3.81	12.10/ 12.13

Example 130:

2-(4-aminophenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester

In 100 ml acetic acid was suspended 2.00 g 2-(4-nitrophenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester, the suspension was heated to 90-100°C. Next, thereto was added 3.00 g iron powder, thereafter, the mixture was heated to the same temperature for 1 hour. The insolubles were eliminated by filtration, thereafter the filtrate was concentrated under reduced pressure. The residue was poured in water, the precipitate was recovered by filtration, recrystallized from dimethylformamide, and thereby 1.46 g of 2-(4-aminophenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester having melting point of 280-285°C was obtained.

Elemental analysis value (%)	as $C_{14}H_{12}N_4O_3S$		
Calculated:	C: 53.15	H: 3.83	N: 17.71
Measured:	C: 52.77	H: 3.96	N: 17.58

Example 131:

2-(5-bromo-2-thienyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester

To a mixture of 3.00 g 2-(2-thienyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester, 5.00 g sodium acetate and 50 ml acetic acid, was added 2.0 ml bromine, the mixture was gently refluxed for 4 hours. After cooling, water was added, and the mixture was stirred at room temperature for 30 minutes. The precipitate was recovered by filtration, recrystallized from dimethylformamide, and thereby 2.48 g of 2-(5-bromo-2-thienyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester having melting point of 261-262°C was obtained.

Elemental analysis value (%)	as $C_{12}H_8BrN_3O_3S_2$		
Calculated:	C: 37.41	H: 2.09	N: 10.91
Measured:	C: 37.76	H: 2.11	N: 10.82

Example 132:

2-(2-chloridephenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid

To 5.5 ml concentrated sulfuric acid was added 2-(2-chloridephenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester, the mixture was heated to 110-120°C. After cooling, the reaction mixture was poured in iced water, the precipitate was recovered by filtration, recrystallized from dimethylformamide, and thereby 1.90 g of 2-(2-chloridephenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid was obtained.

Elemental analysis value (%)	as $C_{12}H_6ClN_3O_3S$		
Calculated:	C: 46.84	H: 1.97	N: 13.66
Measured:	C: 46.78	H: 2.06	N: 13.82

In the same way as in Example 132, the following compounds of formula (I) were produced (wherein, R^1 = -COOH).

Ex. No.	R2	mp. (°C)	Molecular formula	Elemental analysis value Calculated/Measured C	H	N
133	3-chlorophenyl	230-233	C12H5ClN3O3S	46.84/ 46.86	1.97/ 2.43	13.67/ 13.45
134	4-chlorophenyl	281-284	C12H5ClN3O3S	46.84/ 46.76	1.97/ 2.15	13.66/ 13.78
135	3,4-dichlorophenyl	234-238	C12H5Cl2N3O3S	42.12/ 41.90	1.47/ 1.62	12.28/ 12.20
136	3,5-dichlorophenyl	264-268	C12H5Cl2N3O3S	42.12/ 42.42	1.47/ 1.79	12.28/ 12.33
137	4-nitrophenyl	263-266	C12H6N4O5S	45.28/ 45.64	1.90/ 1.77	17.60/ 17.90
138	4-aminophenyl	>300	C12H6N4O3S	49.99/ 49.89	2.80/ 2.83	19.44/ 19.50
139	2-pyridinyl	>310	C11H6N4O3S	48.17/ 48.26	2.21/ 2.49	20.43/ 20.57
140	3-pyridinyl	293-295	C11H6N4O3S	48.17/ 48.11	2.21/ 2.29	20.43/ 20.48
141	4-pyridinyl	>310	C11H6N4O3S	48.17/ 48.21	2.21/ 2.63	20.43/ 20.38
142	6-methyl-2-pyridinyl	290-292	C12H8N4O3S	49.99/ 50.01	2.80/ 2.90	19.44/ 19.49

Example 143:

2-(2-furyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid

A mixture of 1.50 g 2-(2-furyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester, 10 ml trifluoroacetic acid and 10 ml of 47 % hydrobromic acid was heated and stirred at 100°C for 2 hours. Trifluoroacetic acid was eliminated by distillation under reduced pressure and water was added to the residue. The precipitate was recovered by filtration, recrystallized from dimethylformamide, and thereby 0.59 g of 2-(2-furyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid having melting point of 290-293°C was obtained.

Elemental analysis value (%)	as $C_{10}H_5N_3O_4S$		
Calculated:	C: 45.68	H: 2.13	N: 15.96
Measured:	C: 45.53	H: 2.12	N: 16.06

In the same way as in Example 143, the following compounds of formula (I) were produced (wherein, R^1 = -COOH).

Ex. No.	R2	mp. (°C)	Molecular formula	Elemental analysis value Calculated/Measured C	H	N
144	4-methoxyphenyl	245-246	C13H9N3O4S	51.48/ 51.52	2.99/ 2.97	13.86/ 13.88
145	3-fluorophenyl	276-278	C12H6FN3O3S	49.48/ 49.76	2.08/ 2.24	14.43/ 14.60
146	4-fluorophenyl	>300	C12H6FN3O3S	49.48/ 49.72	2.08/ 2.46	14.43/ 14.42
147	4-chloro-3-methylphenyl	223-225	C13H6ClN3O3S	48.58/ 48.57	2.51/ 2.67	13.06/ 12.94
148	2-naphthyl	285-287 (decomp.)	C16H9N3O3S	59.43/ 59.64	2.81/ 3.13	13.00/ 13.22
149	5-chloro-2-furyl	290-298 (decomp.)	C10H4ClN3O4S	40.35/ 40.37	1.35/ 1.65	14.16/ 13.83
150	5-bromo-2-furyl	300-305 (decomp.)	C10H4BrN3O4S	35.21/ 35.60	1.18/ 1.63	12.32/ 12.61
151	2-thienyl	294-296	C10H5N3O3S2	13.00/ 42.96	1.80/ 2.11	15.05/ 15.23
152	5-methyl-2-thienyl	293-298	C11H7N3O3S2	45.04/ 44.93	2.41/ 2.46	14.33/ 14.13
153	5-bromo-2-thienyl	303-305	C10H4BrN3O3S2	33.62/ 33.85	1.29/ 1.35	11.76/ 11.86

Example 154:

2-cyclohexyl-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid

To 55 ml of 0.2 N sodium hydroxide liquid was added 3.10 g 2-cyclohexyl-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester, and the mixture was stirred at room temperature for 1.5 hours. The insolubles were eliminated by filtration, the filtrate was made acidic with dilute hydrochloric acid. The precipitate was recovered by filtration, recrystallized from isopropanol, and thereby 2.00 g of 2-cyclohexyl-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid having pmt of 164-166°C was obtained.

Elemental analysis value (%)	as $C_{12}H_{13}N_3O_3S$		
Calculated:	C: 51.60	H: 4.69	N: 15.04
Measured:	C: 51.77	H: 4.94	N: 14.80

In the same way as in Example 154, the following compounds of formula (I) were produced (wherein, R^1 = -COOH).

Ex. No.	R2	mp. (°C)	Molecular formula	Elemental analysis value Calculated/Measured C	H	N
155	tertiary butyl	295-297 (decomp.)	C10H11N3O3S	47.42/ 47.37	4.38/ 4.55	16.59/ 16.66
156	octyl	115-117	C14H10N3O3S	54.35/ 54.21	6.19/ 5.98	13.58/ 13.72
157	3-hydroxyphenyl	>300	C12H7N3O4S	49.82/ 49.75	2.44/ 2.61	14.53/ 14.63
158	4-hydroxyphenyl	>300	C12H7N3O4S	49.82/ 50.01	2.44/ 2.10	14.53/ 15.04
159	4-hydroxy-3-methoxy phenyl	259-263 (decomp.)	C13H9N3O5S	48.90/ 48.55	2.84/ 2.87	13.16/ 13.13

Example 160:

2-(3,4-methylene dioxyphenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid

To 20 ml of mixed liquid of concentrated hydrochloric acid - 90 % acetic acid (1:11) was added 1.00 g 2-(3,4-methylene dioxyphenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester, the mixture was heated to 80-90°C for 4 hours. After cooling, ethanol was added, the precipitate was recovered by filtration, recrystallized from dimethylformamide - ethanol, and thereby 0.89 g of 2-

(3,4-methylene dioxyphenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid having melting point of 287-290°C was obtained.

Elemental analysis value (%)	as $C_{13}H_7N_3O_5S$		
Calculated:	C: 49.21	H: 2.22	N: 13.25
Measured:	C: 49.45	H: 2.26	N: 13.33

In the same way as in Example 160, the following compounds of formula (I) were produced (wherein, R^1 = -COOH).

Ex. No.	R2	mp. (°C)	Molecular formula	Elemental analysis value Calculated/Measured C	H	N
161	2,3-dimethoxy phenyl	256-259	C14H11N3O5S	50.44/ 50.72	3.33/ 3.47	12.61/ 12.70
162	3,4-dimethoxy phenyl	233-235	C14H11N3O5S	50.44/ 50.76	3.33/ 3.57	12.61/ 12.52
163	3,4,5-trimethoxy phenyl	241-243	C15H31N3O5S	49.58/ 49.65	3.61/ 3.74	11.57/ 11.60
164	3-fluoro-4-methoxy phenyl	270-273	C13H6FN3O4S	48.60/ 48.18	2.51/ 2.56	13.08/ 13.04

Example 165:

2-phenyl-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid

To 2.40 g 2-phenyl-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester was added 40 ml mixed liquid of acetic acid - concentrated hydrochloric acid (9:1), the mixture was heated to 100°C for 1.5 hours. After cooling, water was added, the precipitate was recovered by filtration, recrystallized from dimethylformamide, and thereby 0.95 g of 2-phenyl-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid having melting point of 271-274°C was obtained.

Elemental analysis value (%)	as $C_{12}H_7N_3O_3S$		
Calculated:	C: 52.74	H: 2.58	N: 15.38
Measured:	C: 52.95	H: 2.64	N: 15.46

Example 166:

In the same way as in Example 165, a compound of formula (1) wherein R^2 was 2-chloro-6-fluorophenyl group and R^1 was carboxyl group, was obtained. Melting point, 266-270°C.

Elemental analysis value (%)	as $C_{12}H_5ClFN_3O_5S$		
Calculated:	C: 44.25	H: 1.55	N: 12.90
Measured:	C: 43.62	H: 1.75	N: 12.94

Example 167:

2-(4-methylphenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid

In 10 ml dichloromethane was dissolved 0.90 g 2-(4-methylphenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate methyl ester. Under ice cooling, thereto were added 1.00 g aluminium chloride and 1 ml dimethyl sulfide, and the mixture was stirred at room temperature overnight. Under reduced pressure, low boiling point substances were eliminated, dilute hydrochloric acid was added to the residue. The precipitate was recovered by filtration, recrystallized from dimethylformamide - ethanol, and thereby 0.65 g of 2-(4-methylphenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid having melting point of 280°C was obtained.

Elemental analysis value (%)	as $C_{13}H_9N_3O_3S$		
Calculated:	C: 54.35	H: 3.16	N: 14.66
Measured:	C: 54.32	H: 3.40	N: 14.56

Example 168:

In the same way as in Example 167, a compound of formula (1) wherein R^2 was 4-t-butylphenyl group and R^1 was carboxyl group, was obtained. Melting point, 205°C.

Elemental analysis value (%)	as $C_{16}H_{15}N_3O_5S$		
Calculated:	C: 58.34	H: 4.59	N: 12.76
Measured:	C: 58.18	H: 4.73	N: 12.62

Example 169:

2-(2-fluorophenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid

To a mixed liquid of 10 ml acetic acid and 2.5 ml of 48 % hydrobromic acid was added 1.50 g 2-(2-fluorophenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylate ethyl ester, and the mixture was heated to 120°C for 4 hours. After cooling, the precipitate was recovered by filtration, recrystallized from dimethylformamide, and thereby 0.47 g of 2-(2-fluorophenyl)-5H-5-oxo-[1,3,4] thiadiazolo [3,2-a] pyrimidine-6-carboxylic acid having melting point of over 300°C was obtained.

Elemental analysis value (%)	as $C_{12}H_6FN_3O_5S$		
Calculated:	C: 49.48	H: 2.08	N: 14.43
Measured:	C: 49.17	H: 2.28	N: 14.48

Example 170:

PCA reaction test

The PCA test was carried out as follows. In dorsal part of Sprag-Dowley male rats (CD-SD strain, Japan Charles River) of body weight 170-220 g, was intracutaneously administered 0.05 ml of antiserum which had been diluted 4 times with physiological saline. After 48 hours, PCA reaction was provoked by intravenous administration of 1 ml of 0.5 % Evans blue physiological saline containing 5 mg ovalbumin.. On 30 minutes after the provocation, the rats were decapitated and bled to death, dorsal skin was isolated, the area of blue dye spots (dye leakage mark) was measured from the reverse side thereof.

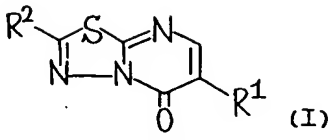
To the drug administration group, the test compound was suspended in 0.5 % CMC liquid, and orally administered to each rat in an amount of 50 mg/body weight kg on 30 minutes before provoking injection. On the other hand, only 0.5 % CMC liquid was administered to the control group.

The PCA reaction suppression rate of the drug administration group was determined by the following equation.

PCA reaction suppression rate (%)
= (Av. blue spot area of control) - (Av. blue spot area of dosing group) x 100
(Av. blue spot area of control group)

Moreover, the antiserum having reaginic antibody with respect to ovalbumin was obtained by a process wherein ovalbumin of 1 mg per rat was dissolved in physiological saline and intramuscularly administered to CD-SD male rats of body weight 300-350 g, and also dead bodies of Bordetella pertussis of 2 - 2.5 x 10^{10} bodies was suspended in physiological saline and intraperitoneally administered, and on 12-14 days later blood was collected and serum was isolated. When the antibody titer of this antiserum was examined by a method wherein intracutanous sensitization was carried out with 0.05 ml on 48-72 hours before antibody injection, and the maximum number of dilution that could induce blue dye spot (dye leakage mark) of diameter 5 mm or more, as a result the antibody titer was 128 times.

The PCA reaction suppression rates of test compounds, namely the compounds of this invention and sodium cromoglycate are shown in the table below.



(I)

Test comp. No.	R2	R1	PCA suppression rate (%)
1	tertiary butyl	1 or 2H-tetrazol-5-yl	48
2	3,4-dichlorophenyl	1 or 2H-tetrazol-5-yl	46
3	2-thienyl	1 or 2H-tetrazol-5-yl	38
4	cyclohexyl	1 or 2H-tetrazol-5-yl	37
5	4-methoxy phenyl	1 or 2H-tetrazol-5-yl	45
6	3,4,5-trimethoxy phenyl	1 or 2H-tetrazol-5-yl	50
7	2-naphthyl	1 or 2H-tetrazol-5-yl	32
8	3-fluorophenyl	1 or 2H-tetrazol-5-yl	36
9	4-fluorophenyl	1 or 2H-tetrazol-5-yl	73
10	3-chlorophenyl	1 or 2H-tetrazol-5-yl	31
11	2-furyl	1 or 2H-tetrazol-5-yl	31
12	5-methyl-2-thienyl	1 or 2H-tetrazol-5-yl	32
13	2-pyridyl	1 or 2H-tetrazol-5-yl	34
14	4-pyridyl	1 or 2H-tetrazol-5-yl	32
15	phenyl	1 or 2H-tetrazol-5-yl	43
16	4-tert-butylphenyl	1 or 2H-tetrazol-5-yl	32
17	2-thienyl	ethoxy carbonyl	32
18	4-fluorophenyl	methoxy carbonyl	33
19	4-methoxy phenyl	ethoxy carbonyl	34
20	4-fluorophenyl	ethoxy carbonyl	34
21	4-methoxy phenyl	methoxy carbonyl	40
22	cyclohexyl	carboxyl	35
23	2-chlorophenyl	carboxyl	31
24	4-methylphenyl	carboxyl	30
25	2,3-dimethoxy phenyl	carboxyl	39
26	3,4,5-trimethoxy phenyl	carboxyl	32
27	4-chlorophenyl	carboxyl	30
28	3,4-dichlorophenyl	carboxyl	30
29	2-pyridyl	carboxyl	30
30	4-fluorophenyl	carboxyl	63
31	2-thienyl	carboxyl	41
32	4-tert-butylphenyl	carboxyl	31
33	disodium cromoglycate (300 mg/weight kg administration)		0

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